Attorney Docket No. 078728-0104

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Applicants:	Joseph ROBERTS, *et al.*
Title:	**PROTECTING THERAPEUTIC COMPOSITIONS FROM HOST-MEDIATED INACTIVATION**
Appl. No.:	09/972,245
Filing Date:	10/09/2001
Examiner:	Richard A. Schnizer
Art Unit:	1635
Confirmation Number:	3976

REPLY BRIEF

Mail Stop Appeal Brief - Patents
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Sir:

Under the provisions of 37 C.F.R. § 41.41, this Reply Brief is submitted in response to the Examiner's Answer, dated April 22, 2010. Although Appellants believe that no fee is required, authorization is hereby given to charge any deficiency (or credit any balance) to the undersigned deposit account 19-0741.

REAL PARTY IN INTEREST

The named inventors of the above-captioned application have assigned all rights, title, and interest in the invention to the University of South Carolina.

RELATED APPEALS AND INTERFERENCES

No related appeals or interferences are pending.

STATUS OF CLAIMS

Claims 1-6, 11-13, 17-22, 41-42, and 44 are pending, claims 7-10, 14-16, 23-40, 43, 45, and 46 are cancelled, and claims 47-64 are withdrawn from examination. Claims 1-6, 11-13, 17-22, 41-42, and 44 are finally rejected and are the subject of this appeal. The pending claims are presented in Appendix A of this Reply Brief.

STATUS OF AMENDMENTS

In the Office Action dated June 23, 2009, the PTO entered and considered all of the amendments set forth in the Amendment and Reply Under 37 C.F.R. §1.116 that was filed on May 20, 2009. No amendments were submitted after the Office Action of June 23, 2009.

SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 is directed to a method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer. The method includes the steps of:

(a) assaying a first blood sample from a first immunocompetent subject for a biological activity of a first modified therapeutic agent after said first modified therapeutic agent has been administered to said first immunocompetent subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(b) assaying a second blood sample from said first immunocompetent subject for the biological activity of said first modified therapeutic agent after at least one booster dose of said first modified therapeutic agent has been administered to said first immunocompetent subject;

(c) assaying a third blood sample from a second immunocompetent subject for the biological activity of a second modified therapeutic agent after said second modified therapeutic agent has been administered to said second immunocompetent subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(d) assaying a fourth blood sample from said second immunocompetent subject for the biological activity of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said second immunocompetent subject; and

(e) comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer,

wherein said therapeutic agent comprises an enzyme and said biological activity comprises an enzyme catalyzing a reaction, and

wherein said assaying comprises measuring the extent to which said first modified therapeutic agent and said second modified therapeutic agent catalyze a reaction. *See* Specification, page 13, lines 4- 26 and page 21, line 7 to page 23, line 7. In some aspects, the biocompatible polymer can be a polyethylene glycol ("PEG") which is selected from the group consisting of mono-methoxy succinimidyl butanoate (SBA)-PEG, succinimidyl carbonate (SC)-PEG, aldehyde (ALD)-PEG, and succinimidyl propionate (SPA)-PEG. *Id.* at page 15, lines 12-20.

Claim 17 depends from claim 1 and concerns a method of preparing a pharmaceutical composition where host-mediated inactivation is prevented. The inventive method comprises selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent by the method of claim 1 and modifying said therapeutic agent according to the type of biocompatible polymer, the extent of modification, and the conditions for modification selected. *Id.* at page 18, lines 4-6 and page 23, lines 1-7.

Independent claim 42 is directed to a method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer, comprising:

(a) selecting a biological activity;

(b) assaying a first blood sample from a first immunocompetent subject for the selected biological activity of step (a) of a first modified therapeutic agent after said first modified therapeutic agent has been administered to said first immunocompetent subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(c) assaying a second blood sample from said first immunocompetent subject for the selected biological activity of step (a) of said first modified therapeutic agent after at least

one booster dose of said first modified therapeutic agent has been administered to said first immunocompetent subject;

(d) assaying a third blood sample from a second immunocompetent subject for the selected biological activity of step (a) of a second modified therapeutic agent after said second modified therapeutic agent has been administered to said second immunocompetent subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(e) assaying a fourth blood sample from said second immunocompetent subject for the selected biological activity of step (a) of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said second immunocompetent subject; and

(f) comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer,

wherein said therapeutic agent comprises an enzyme and said biological activity comprises an enzyme catalyzing a reaction and

wherein said assaying comprises measuring the extent to which said first modified therapeutic agent and said second modified therapeutic agent catalyze a reaction.

Id. at page 13, lines 4- 26 and page 21, line 7 to page 23, line 7.

Yet another aspect of the presently claimed invention provides, as recited in independent claim 44, a method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when

covalently modified by said biocompatible polymer. The method includes the following steps:

(a) selecting a biological activity;

(b) assaying a first blood sample from a first immunocompetent subject for the selected biological activity of step (a) of a first modified therapeutic agent after said first modified therapeutic agent has been administered to said first immunocompetent subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(c) assaying a second blood sample from said first immunocompetent subject for the selected biological activity of step (a) of said first modified therapeutic agent after at least one booster dose of said first modified therapeutic agent has been administered to said first immunocompetent subject;

(d) assaying a third blood sample from a second immunocompetent subject for the selected biological activity of step (a) of a second modified therapeutic agent after said second modified therapeutic agent has been administered to said second immunocompetent subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(e) assaying a fourth blood sample from said second immunocompetent subject for the selected biological activity of step (a) of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said second immunocompetent subject;

(f) comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to determine the relative bioavailability of said first modified therapeutic agent and said second therapeutic agent; and

(g) selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer based upon the comparison of step (f),

wherein said therapeutic agent comprises an enzyme and said biological activity comprises an enzyme catalyzing a reaction and

wherein said assaying comprises measuring the extent to which said first modified therapeutic agent and said second modified therapeutic agent catalyze a reaction. *Id.*

GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The rejections to be reviewed on appeal are whether claims 1-3, 5-6, 12, 13, 17, 18, 41, 42, and 44 are unpatentable under 35 U.S.C. § 103(a) over the combination of Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, and Francis *et al.*; whether claim 4 is unpatentable under 35 U.S.C. § 103(a) over the combination of Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, Francis *et al.* and Petersen et al.; whether claims 8, 11 and 20-22 are unpatentable under 35 U.S.C. § 103(a) over the combination of Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, Francis *et al.*, and Abuchowski *et al.*; and whether claim 19 is unpatentable under 35 U.S.C. § 103(a) over the combination of Boos *et al.*, Kawashima *et al.*, Ettinger *et al.*, Saito *et al.*, Francis *et al.* and Bollin *et al.*

ARGUMENT

Pursuant to 37 C.F.R. §41.41, Appellants take this opportunity to respond to certain comments in the Examiner's Answer dated April 22, 2010 ("Answer").

I. The prior art does not inherently fulfill the purpose of the claimed methods

The Examiner states that, "[i]f one compared treatment protocols with two differently modified asparaginases," per the asserted combination the Boos and Saito references, etc., "then one would have carried out the same active method steps that Applicant claims" and, hence, "inherently [would have] fulfilled the purpose set forth in the preamble" of appealed claims. Answer at page 9, first full paragraph. The context of the claimed invention, however, resides in the identification of a modification to a therapeutic agent, not in identifying a superior agent, *per se*. Accordingly, the method of the claimed invention utilizes steps differing from those reasonably gleaned from the prior art, and achieves a different result, too.

First, the cited references either compare two unmodified asparaginases or one modified and one unmodified asparaginase, and not two modified therapeutic agents, as recited in (a) – (e) of the appealed claims. In contrast, the steps in Boos, Kawashima, Saito, and Ettinger would not have identified which *type* of biocompatible polymer should be used for a therapeutic agent, because only one type of biocompatible polymer, if any, was used in each of the prior-art comparison steps. Even in view of Francis, moreover, the skilled artisan would not have been motivated to combine the references, thereby to come up with an evaluation of two modified agents, because the comparison in the art always pertains to the reference unmodified agent.

Likewise, the *extent* of modification would not be assessed by the prior art because the art does not evaluate two modified therapeutic agents that differ in range of modification. The same rationale applies to the conditions for modification.

Second, the prior art would not have identified which type of biocompatible polymer, the extent of modification and the conditions for modification to prevent host-mediated

inactivation, which the claimed invention does, because the art does not teach a step in which these specific modification variables are compared and then selected, as recited in (e) of the appealed claims. Indeed, the methods in the prior art only identify in absolute terms which therapeutic agent, based on a comparison of two compounds, yielded a greater therapeutic benefit, and do not ascertain information regarding the modification features relevant to preventing host-mediated inactivation. Thus, the art does not consider an analysis as to *why* one agent is better than another therapeutic agent, much less consider applying that information to create a potentially more optimal therapeutic agent.

In summary, the information extracted from the prior art methods is distinct from the information obtained by performing the method steps of the claimed invention, and the selection step in particular. The methods of the cited references do not inherently fulfill the purpose of the claimed invention, therefore, and do not suggest the salient steps recited in the appealed claims.

II. Patentability of the claimed method must be assessed in a preclinical context

"To the extent that Applicant's [*sic*] argument relies on any distinction between clinical and preclinical settings," the Examiner states, "it is unpersuasive because the claims do not recite any limitations regarding clinical or preclinical settings." Answer at page 19, first full paragraph. This position is unquestionably flawed, however, given the plain meaning of the claims and the teachings in the specification.

The claims are directed to a method for identifying information relevant to preventing host-mediated inactivation (*i.e.*, type of biocompatible polymer, extent of modification, and conditions for modification) and to selecting those factors that prevent such inactivation, ultimately to create a suitably modified therapeutic agent. Because the recited identification of the type of biocompatible polymer, extent of modification, and conditions for modification for a therapeutic agent could only occur before the modified therapeutic is selected for use in a clinical setting, it is apparent that the claimed invention is a therapeutic optimization scheme.

It necessarily follows, therefore, that the claimed invention occurs in the preclinical context, whence the patentability of the invention must be assessed. Indeed, the Examiner's refusal to conduct his analysis accordingly is the fundamental error warranting reversal of the appealed rejections.

III. Preventing host-mediated inactivation directly influences the claimed selection step

The Examiner contends that "the weight of the preamble's stated objective reduces to whether or not the preamble's intended use limitation 'to prevent host-mediated inactivation' distinguishes over the prior art," and that "[t]here is no manipulative step that is affected in any way by the preamble's recitation of the intended use . . . ." Answer at page 22, first paragraph. Yet, *preventing* host-mediated inactivation is not a factor in any conventional methodology. By contrast, it is the variable that informs the selection step of the claimed invention.

The prior art measures asparaginase biological activity in the context of a treatment protocol for patients suffering, for example, from acute lymphoblastic anemia, and compares the candidates to identify which one had a greater therapeutic effect. The references, however, do not contemplate modifications to agents for *preventing* a particular host-mediated effect. To the contrary, the therapeutic candidates in the art have been selected already, regardless of their ability to prevent host-mediated inactivation.

"Host-mediated inactivation" goes unmentioned and unconsidered in the prior art, but it is *the* important feature of the claimed invention. Thus, the claims recite several manipulative steps for assaying blood samples for biological activity of two or modified therapeutic agents and, importantly, recite an additional step of selecting modifications as a function of their ability to prevent host-mediated inactivation. Rather than a purported "intended use," as the Examiner asserts, the preventing of host-mediated inactivation is integrally related to the manipulative step of selecting suitable modification variables in accordance with the claimed invention.

CONCLUSION

In view of these remarks and its previous appeal brief, appellant respectfully renews its requests that the rejections be reversed in whole and that the claims be allowed to issue.

Respectfully submitted,

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APPENDIX A: CLAIMS INVOLVED IN APPEAL

1. (Previously Presented) A method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer, comprising:

(a) assaying a first blood sample from a first immunocompetent subject for a biological activity of a first modified therapeutic agent after said first modified therapeutic agent has been administered to said first immunocompetent subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(b) assaying a second blood sample from said first immunocompetent subject for the biological activity of said first modified therapeutic agent after at least one booster dose of said first modified therapeutic agent has been administered to said first immunocompetent subject;

(c) assaying a third blood sample from a second immunocompetent subject for the biological activity of a second modified therapeutic agent after said second modified therapeutic agent has been administered to said second immunocompetent subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(d) assaying a fourth blood sample from said second immunocompetent subject for the biological activity of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said second immunocompetent subject; and

(e) comparing the biological activity of said first modified therapeutic agent with the biological activity of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that

prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer,

wherein said therapeutic agent comprises an enzyme and said biological activity comprises an enzyme catalyzing a reaction, and

wherein said assaying comprises measuring the extent to which said first modified therapeutic agent and said second modified therapeutic agent catalyze a reaction.

2. (Previously Presented) The method of claim 1, wherein said second modified therapeutic agent is modified with the same biocompatible polymer as said first modified therapeutic agent.

3. (Previously Presented) The method of claim 2, wherein said biocompatible polymer is polyethylene glycol (PEG).

4. (Original) The method of claim 3, wherein said PEG is selected from the group consisting of mono-methoxy succinimidyl butanoate (SBA)-PEG, succinimidyl carbonate (SC)-PEG, aldehyde (ALD)-PEG, and succinimidyl propionate (SPA)-PEG.

5. (Previously Presented) The method of claim 1, wherein said second modified therapeutic agent is modified to the same extent as said first modified therapeutic agent.

6. (Previously Presented) The method of claim 1, wherein said second modified therapeutic agent and said first modified therapeutic agent are modified with different biocompatible polymers.

7-10. Cancelled.

11. (Previously Presented) The method of claim 1, wherein said enzyme is used to lower glutamine levels in a subject.

12. (Previously Presented) The method of claim 1, wherein said enzyme is used to lower asparagine levels in a subject.

13. (Previously Presented) The method of claim 1, wherein said enzyme is used to lower asparagine and glutamine levels in a subject.

14-16. Cancelled.

17. (Previously Presented) A method of preparing a pharmaceutical composition where host-mediated inactivation is prevented, comprising selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent by the method of claim 1 and modifying said therapeutic agent according to the type of biocompatible polymer, the extent of modification, and the conditions for modification selected.

18. (Original) The method of claim 17, wherein said pharmaceutical composition further comprises an excipient.

19. (Original) The method of claim 18, wherein said excipient protects said therapeutic agent during lyophilization.

20. (Original) The method of claim 17, wherein said therapeutic agent comprises glutaminase-asparaginase.

21. (Previously Presented) The method of claim 20, wherein said therapeutic agent comprises *Pseudomonas* glutaminase-asparaginase.

22. (Original) The method of claim 21, wherein said *Pseudomonas* glutaminase-asparaginase is modified with polyethylene glycol.

23-40 Cancelled.

41. (Previously Presented) The method of claim 1, wherein said second immunocompetent subject is the same person as said first immunocompetent subject.

42. (Previously Presented) A method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent

with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer, comprising:

(a) selecting a biological activity;

(b) assaying a first blood sample from a first immunocompetent subject for the selected biological activity of step (a) of a first modified therapeutic agent after said first modified therapeutic agent has been administered to said first immunocompetent subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(c) assaying a second blood sample from said first immunocompetent subject for the selected biological activity of step (a) of said first modified therapeutic agent after at least one booster dose of said first modified therapeutic agent has been administered to said first immunocompetent subject;

(d) assaying a third blood sample from a second immunocompetent subject for the selected biological activity of step (a) of a second modified therapeutic agent after said second modified therapeutic agent has been administered to said second immunocompetent subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(e) assaying a fourth blood sample from said second immunocompetent subject for the selected biological activity of step (a) of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said second immunocompetent subject; and

(f) comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to select the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer,

wherein said therapeutic agent comprises an enzyme and said biological activity comprises an enzyme catalyzing a reaction and

wherein said assaying comprises measuring the extent to which said first modified therapeutic agent and said second modified therapeutic agent catalyze a reaction.

43. Cancelled.

44. (Previously Presented) A method for determining the type of biocompatible polymer, the extent of modification, and the conditions for modification of a therapeutic agent with a biocompatible polymer to prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer, comprising:

(a) selecting a biological activity;

(b) assaying a first blood sample from a first immunocompetent subject for the selected biological activity of step (a) of a first modified therapeutic agent after said first modified therapeutic agent has been administered to said first immunocompetent subject, wherein said first modified therapeutic agent is covalently modified with a biocompatible polymer;

(c) assaying a second blood sample from said first immunocompetent subject for the selected biological activity of step (a) of said first modified therapeutic agent after at least one booster dose of said first modified therapeutic agent has been administered to said first immunocompetent subject;

(d) assaying a third blood sample from a second immunocompetent subject for the selected biological activity of step (a) of a second modified therapeutic agent after said second modified therapeutic agent has been administered to said second immunocompetent subject, wherein said second modified therapeutic agent is covalently modified with a biocompatible polymer and wherein at least one condition selected from the group consisting of the type of biocompatible polymer, the extent of modification, and the conditions for modification differs from the conditions of said first modified therapeutic agent;

(e) assaying a fourth blood sample from said second immunocompetent subject for the selected biological activity of step (a) of said second modified therapeutic agent after at least one booster dose of said second modified therapeutic agent has been administered to said second immunocompetent subject;

(f) comparing the selected biological activity of step (a) of said first modified therapeutic agent with the selected biological activity of step (a) of said second modified therapeutic agent to determine the relative bioavailability of said first modified therapeutic agent and said second therapeutic agent; and

(g) selecting the type of biocompatible polymer, the extent of modification, and the conditions for modification that prevent host-mediated inactivation of said therapeutic agent when covalently modified by said biocompatible polymer based upon the comparison of step (f),

wherein said therapeutic agent comprises an enzyme and said biological activity comprises an enzyme catalyzing a reaction and

wherein said assaying comprises measuring the extent to which said first modified therapeutic agent and said second modified therapeutic agent catalyze a reaction.

45-46. Cancelled.

47. (Withdrawn) The pharmaceutical composition prepared by the method of claim 17, wherein said pharmaceutical composition comprises a glutaminase-asparaginase that has been modified with succinimidyl carbonate polyethylene glycol 5000 (SC-PEG 5000), wherein said glutaminase-asparaginase is modified to an extent of from about 21% to about 49% by SC-PEG 5000, and wherein said composition prevents host-mediated inactivation.

48. (Withdrawn) The composition of claim 47, wherein said glutaminase-asparaginase is modified from about 26% to about 36% by SC-PEG 5000.

49. (Withdrawn) The composition of claim 48, wherein said glutaminase-asparaginase is modified about 31% by SC-PEG 5000.

50. (Withdrawn) The pharmaceutical composition prepared by the method of claim 17, wherein said pharmaceutical composition comprises a glutaminase-asparaginase that has been modified with mono-methoxy succinimidyl butanoate polyethylene glycol 5000 (SBA-PEG 5000), wherein said glutaminase-asparaginase is modified from about 25% to about 58% by SBA-PEG 5000, and wherein said composition prevents host-mediated inactivation.

51. (Withdrawn) The composition of claim 50, wherein said glutaminase-asparaginase is modified from about 30% to about 40% by SBA-PEG 5000.

52. (Withdrawn) The composition of claim 51, wherein said glutaminase-asparaginase is modified about 35% by SBA-PEG 5000.

53. (Withdrawn) The pharmaceutical composition prepared by the method of claim 17, wherein said pharmaceutical composition comprises a glutaminase-asparaginase that has been modified with aldehyde polyethylene glycol 2000 (ALD-PEG 2000), wherein said glutaminase-asparaginase is modified from about 45% to about 65% by ALD-PEG 2000, and wherein said composition prevents host-mediated inactivation.

54. (Withdrawn) The pharmaceutical composition prepared by the method of claim 17, wherein said pharmaceutical composition comprises a glutaminase-asparaginase that has been modified with succinimidyl propionate polyethylene glycol 5000 (SPA-PEG 5000), wherein said modified glutaminase-asparaginase is modified from about 25% to about 65% by SPA-PEG 5000, and wherein said composition prevents host-mediated inactivation.

55. (Withdrawn) The composition of claim 54, wherein said glutaminase-asparaginase is modified from about 40% to about 55% by SPA-PEG 5000.

56. (Withdrawn) A composition comprising a glutaminase-asparaginase, wherein said glutaminase-asparaginase has been modified with succinimidyl carbonate polyethylene glycol 5000 (SC-PEG 5000) to an extent of about between 21% and 49%.

57. (Withdrawn) The modified therapeutic composition of claim 56, wherein said glutaminase-asparaginase has been modified to an extent of about between 26% and 36%.

58. (Withdrawn) The modified therapeutic composition of claim 57, wherein said glutaminase-asparaginase has been modified to an extent of about 31%.

59. (Withdrawn) A composition comprising a glutaminase-asparaginase, wherein said glutaminase-asparaginase has been modified with succinimidyl butanoate polyethylene glycol 5000 (SBA-PEG 5000) to an extent of about between 25% and 58%.

60. (Withdrawn) The modified therapeutic composition of claim 59, wherein said glutaminase-asparaginase has been modified to an extent of about 30% to 40%.

61. (Withdrawn) The modified therapeutic composition of claim 36, wherein said glutaminase-asparaginase has been modified to an extent of about 35%.

62. (Withdrawn) A composition comprising a glutaminase-asparaginase, wherein said glutaminase-asparaginase has been modified with aldehyde polyethylene glycol 2000 (ALD-PEG 2000) to an extent of about between 45% and 65%.

63. (Withdrawn) A composition comprising a glutaminase-asparaginase, wherein said glutaminase-asparaginase has been modified with succinimidyl propionate polyethylene glycol 5000 (SPA-PEG 5000) to an extent of about between 25% and 65%.

64. (Withdrawn) The modified therapeutic composition of claim 63, wherein said glutaminase-asparaginase has been modified to an extent of about 40% to 55%.

APPENDIX B. EVIDENCE

None.

APPENDIX C. RELATED PROCEEDINGS

No related proceedings are pending.